10-07-05

AF/1617

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Fred S. Lamb et al.

Title: USE OF CLC3 CHLORIDE CHANNEL BLOCKERS TO MODULATE VASCULAR TONE

Docket No.: 17023.017US1
Filed: August 15, 2001
Examiner: Jennifer M. Kim

Serial No.: 09/930,105
Group Art Unit: 1617

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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APPEAL BRIEF

Mail Stop Appeal Brief - Patents
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Sir:

The Final Office Action for this application was mailed August 24, 2004, and a Notice of Appeal was mailed February 18, 2005. An Appeal Brief was filed on April 18, 2005. However, as indicated in the Notification of Non-Compliant Appeal Brief mailed September 7, 2005, the April 18, 2005 Appeal Brief did not contain the items required under 37 CFR 41.37(c).

Applicants respectfully appeal to the Board for review of the Examiner's final rejection. Applicants also respectfully request that the attorney docket number for this application be changed to 17023.017US1.

(1) Real Party in Interest.

The real party in interest is the University of Iowa Research Foundation.

(2) Related Appeals and Interferences.

Application Serial No. 09/512,926, to which the instant application claims priority, is also currently being appealed to the Board for review of the Examiner's final rejection. There are no related interferences.

(3) Status of Claims.

Claims 22-24, 27-29, 31-35 and 38-43 are currently pending. Claims 1-21, 25-26, 30 and 36-37 have been canceled. Claims 22-24, 27-29, 31-35 and 38-43 stand finally rejected. Applicants are appealing the final rejection of claims 22-24, 27-29, 31-35, and 38-43.

(4) Status of Amendments.

An Amendment and Reply was filed on November 2, 2004. In the Advisory Action mailed November 26, 2004, the Examiner indicated that the November 2, 2004 Amendment and Reply will be entered for the purposes of appeal.

(5) Summary of the Claimed Subject Matter.

The claimed subject matter relates to methods for modulating vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction, as well as methods for modulating penile vascular tone in a mammal in need thereof. The methods include administering a pharmaceutically effective amount of a chloride channel blocking agent or a pharmaceutically acceptable salt thereof. The claimed subject matter also relates to a method for treating erectile dysfunction, wherein the method includes administering a composition containing a CLC3 channel blocking agent or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. This subject matter is described throughout the specification, for example, at page 6, line 25 through page 14, line 9.

(6) Grounds of Rejection to be Reviewed on Appeal.

The issues being appealed are: (1) whether claims 22-24, 27-29, 33-35 or 39-43 are anticipated under 35 U.S.C. § 102(b) by Delaney *et al.* (Delaney *et al.*, (1996) *The Breast* 5:53-54) as evidenced by U.S. Patent No. 5,658,936 (the Kifor *et al.* patent); and (2) whether claims 31, 32 or 38 are unpatentable under 35 U.S.C. § 103(a) over Delaney *et al.* in view of U.S. Patent No. 6,266,560 (the Zhang *et al.* patent) and Drug Facts and Comparisons (1997).

(7) Argument.

A. The claims are not anticipated by Delaney *et al.*

The Examiner alleges that claims 22-24, 27-29, 33-35 and 39-43 are anticipated by Delaney *et al.* as evidenced by the Kifor *et al.* patent. The Examiner stated that Delaney *et al.* clearly teaches that a patient treated with tamoxifen exhibited significantly enhanced libido. The Examiner also stated that the Kifor *et al.* patent provides evidence of the equivalence between improvement in erectile function and increased libido. The Examiner further stated that Applicants' recitation in the claims of a mechanism for modulating penile vascular tone does not represent a patentable limitation, and that tamoxifen has been previously used to obtain the same pharmacological effect (enhanced erection) that would result from the claimed method.

Claims 22-24, 27-29, and 31-32 relate to methods for using a chloride channel blocking agent to modulate vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction. Claims 33-42 relate to methods for using a chloride channel blocking agent to modulate penile vascular tone in a mammal in need thereof. Claim 43 recites a method for treating erectile dysfunction. Applicants respectfully assert that the rejection of the present claims as being anticipated by Delaney *et al.* is incorrect.

First, Delaney *et al.* fails to anticipate the present claims. Delaney *et al.* discloses that one male patient on a tamoxifen regimen had experienced increased libido during his course of treatment. At no point does Delaney *et al.* disclose that the patient had compromised vascular tissue associated with erectile dysfuction, as recited in claims 22-24, 27-29, and 31-32. Further, at no point does Delaney *et al.* disclose that the patient was in need of modulated penile vascular tone as recited in claims 33-35 and 38-42, or was diagnosed with erectile dysfunction as recited in claim 43. While Delaney *et al.* suggests that tamoxifen may have been the cause of the patient's increased libido, Delaney *et al.* fails to even suggest that tamoxifen might be useful to modulate penile vascular tone in a patient with erectile dysfunction.

Second, Delaney *et al.* fails to establish a causative link between tamoxifen treatment and increased libido. Delaney *et al.* discloses that one male cancer patient experienced increased libido during a course of treatment with tamoxifen. According to Delaney *et al.*, the patient began tamoxifen treatment in April of 1993. Ten months later, in February of 1994, he reported that he had experienced significantly enhanced libido for the immediately preceding 6 months. As such, the

onset of increased libido did not occur until the patient had been taking tamoxifen for about four months. Moreover, when the patient was reevaluated in January of 1995, his libido had returned to normal levels despite the fact that he continued tamoxifen treatment. Thus, the perceived side effect of increased libido was not observed until the patient had been on tamoxifen for a relatively long time, and it resolved before the patient discontinued his tamoxifen treatment.

Delaney *et al.* does not report that any studies were conducted to determine whether the tamoxifen treatment was definitively linked to the patient's increase in libido. In addition, Delaney *et al.* did not attempt to establish whether the increased libido might have been linked to any of the other treatments to which the cancer patient had been subjected, including chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil, as well as radiotherapy. In fact, the authors of Delaney *et al.* were unsure as to the cause of the increased libido, as they speculate that it may have been related to the relatively young age of the patient. They do not disclose any evidence that tamoxifen treatment and increased libido were causatively linked.

In addition, Delaney *et al.* discloses that the increase in libido observed in this one patient was contrary to other case reports in which tamoxifen therapy was associated with impotence. In fact, Delaney *et al.* discloses that previous studies had found that 5 to 30 percent of men receiving tamoxifen experienced reduced libido. Thus, Delaney *et al.* clearly teaches that the patient in question was an outlier, and that tamoxifen treatment would be expected to reduce libido rather than to increase libido.

Third, libido and erectile dysfunction are significantly different conditions; an improvement in erectile function cannot be equated with an increase in libido. Libido is a psychological phenomenon that is defined by the Merriam-Webster online dictionary as "emotional or psychic energy that in psychoanalytic theory is derived from primitive biological urges and that is usually goal-directed; or sexual drive." Erectile dysfunction is a physiological condition that is defined by the On-Line Medical Dictionary as "a consistent inability to sustain an erection sufficient for sexual intercourse." Given these differences, increasing libido and modulating penile vascular tone to treat erectile dysfunction are likely accomplished by different mechanisms. Thus, even if tamoxifen treatment was casually linked to increased libido, there would have been no reason to believe that it could be used to modulate penile vascular tone or to treat erectile dysfunction.

The Kifor *et al.* patent is consistent with the above definitions when it states that improved erectile function can include "any enhancement of the ability of a subject to maintain an erection, induce or improve ejaculation, induce or improve orgasm, and increase libido." (*See*, column 7, lines 4-8 of the Kifor *et al.* patent.) Thus, an increase in libido may improve erectile dysfunction, but does not necessarily do so. As such, improved erectile function and increased libido are distinct and cannot be equated.

In summary, given the differences between libido and erectile dysfunction, together with the lack of evidence establishing that tamoxifen treatment was causally associated with one individual's increased libido, as well as the failure of Delaney *et al.* to disclose that tamoxifen would be useful in a patient having compromised vascular tissue and/or erectile dysfunction, it is clear that the cited documents does not anticipate the present claims.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 22-24, 27-29, 33-35, and 39-43 under 35 U.S.C. § 102(b).

B. The claims are patentable over Delaney *et al.* in view of the Zhang *et al.* patent and Drug Facts and Comparisons (1997).

The Examiner alleges that claims 31, 32 and 38 are unpatentable over Delaney *et al.* as applied to claims 22-24, 27-29, 33-35, and 39-43, and further in view of the Zhang *et al.* patent and Drug Facts and Comparisons (1997). The Examiner stated that while Delaney *et al.* does not expressly teach the route of administration set forth in claims 32 and 38, or the further administration of the agents set forth in claim 31, Drug Facts and Comparisons teaches that tamoxifen is commercially available in oral form, while the Zhang *et al.* patent reports that vasodilators are useful for treatment of erectile dysfunction. Thus, the Examiner concluded that it would have been obvious to a person having ordinary skill in the art to administer tamoxifen orally. The Examiner also concluded that it would have been obvious to incorporate a vasodilator agent with tamoxifen because vasodilators are useful for treatment of erectile dysfunction.

Claims 31 and 32 depend from claim 22, and claim 38 depends from claim 33. Thus, these claims relate to methods for using a chloride channel blocking agent to modulate vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction, or to modulate penile vascular tone in a mammal in need thereof. As discussed above, Delaney *et al.* discloses only

that one male patient experienced increased libido during a portion of the time for which he was on a tamoxifen regimen. The patient was disclosed to be a 35 year-old breast cancer patient. At no point was he disclosed to have erectile dysfunction or to be in need of modulated penile vascular tone. Thus, Delaney *et al.* fails to provide any suggestion that tamoxifen might be useful to modulate vascular tone in a patient having compromised vascular tissue.

Moreover, Delaney *et al.* teaches away from using tamoxifen to increase libido. In fact, Delaney *et al.* teach that tamoxifen treatment is more likely to result in reduced libido than increased libido. In addition, libido and erectile function are very different conditions, as described above. Even if libido and erectile dysfunction could be equated, which they cannot, a subject having erectile dysfunction or compromised penile vascular tissue surely would not have been motivated by Delaney *et al.* to use tamoxifen to treat his condition. This is particularly true given the four-month lag time between administration of tamoxifen and the reported onset of increased libido, as well as the reduction in libido to normal levels prior to discontinuation of tamoxifen therapy. As such, a person of ordinary skill in the art reading Delaney *et al.* would not have been motivated to use a chloride channel blocking agent such as tamoxifen to modulate vascular tone in a patient, or to modulate penile vascular tone in a mammal in need thereof.

The Zhang *et al.* patent and the Drug Facts and Comparisons document fail to remedy the deficiencies of Delaney *et al.*. At no point do either of these documents suggest that a chloride channel blocking agent such as tamoxifen would be useful either to modulate vascular tone in a patient having compromised vascular tissue associated with erectile dysfunction or to modulate penile vascular tone in a mammal in need thereof. Moreover, at no point does the combination of Delaney *et al.* with the Zhang *et al.* patent and the Drug Facts and Comparisons document suggest that a chloride channel blocker would be useful to modulate vascular tone either alone or in combination with another agent (*e.g.*, a vasodilator), regardless of how it was administered. Thus, the combination of these three documents fails to render claims 31, 32, and 38 obvious.

In light of the above, Applicants respectfully request reversal of the Examiner's rejection of claims 31, 32, and 38 under 35 U.S.C. § 103(a).

If necessary, please charge any additional fees or credit overpayment to Deposit Account 50-3503.

Respectfully submitted,

Fred S. Lamb et al.

By their Representatives,

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Date: 6 October 2005

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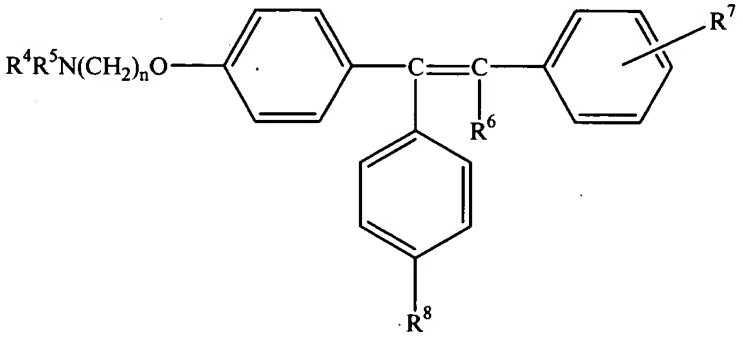
"Express Mail" mailing label number: EV703160235
Date of Deposit: October 6, 2005
It is certified that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicates above and is addressed to Mail Stop Appeal Brief - Patent, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

(8) Claims Appendix.

22. A method to modulate vascular tone in a patient having compromised vascular tissue, comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof, wherein the compromised vascular tissue is associated with erectile dysfunction.

23. A method of claim 22, wherein the chloride channel blocking agent is a compound of Formula I



I

wherein either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical;

R^6 is H or a lower alkyl radical;

R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical;

R^8 is H or OH; and

n is 2;

or a pharmaceutically acceptable salt thereof.

24. A method of claim 23, wherein the compound is 1-p-β-dimethylaminoethoxyphenyl-trans-1,2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof.

27. A method of claim 22, wherein the chloride channel is a CLC3 channel.

28. The method of claim 27, wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine.

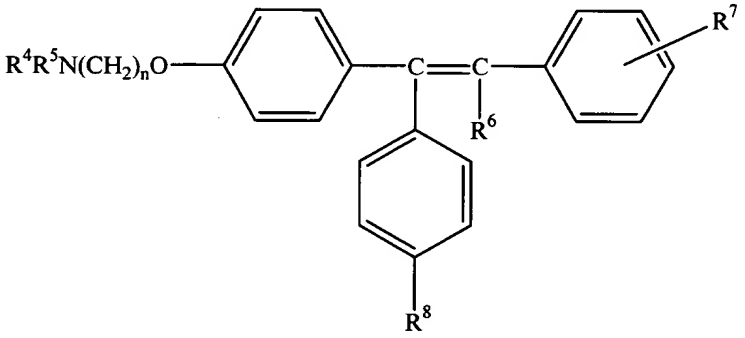
29. The method of claim 22, wherein the agent modulates vascular tone by enhancing vasodilation.

31. A method of claim 22, further comprising administering a pharmaceutically effective compound selected from an anti-diabetes agent, an anti-hypertension agent, an anti-coronary artery disease agent, an anti-restenosis agent, and a vasodilatory agent.

32. A method of claim 22, wherein the agent is administered intravenously or orally.

33. A method to modulate penile vascular tone in a mammal in need thereof, said method comprising administering a pharmaceutically effective amount of a chloride channel blocking agent, or a pharmaceutically acceptable salt thereof.

34. A method of claim 33, wherein the chloride channel blocking agent is a compound of Formula I



I

wherein either R^4 is H or a lower alkyl radical and R^5 is a lower alkyl radical, or R^4 and R^5 are joined together with the adjacent nitrogen atom to form a heterocyclic radical;

R^6 is H or a lower alkyl radical;

R^7 is H, halo, OH, a lower alkyl radical, or is a buta-1,3-dienyl radical which together with the adjacent benzene ring forms a naphthyl radical;

R^8 is H or OH; and

n is 2;

or a pharmaceutically acceptable salt thereof.

35. A method of claim 34, wherein the compound administered is 1-p-β-dimethylaminoethoxyphenyl-trans-l, 2-diphenylbut-1-ene, or a pharmaceutically acceptable salt thereof.

38. The method of claim 33, wherein the agent is administered orally or intravenously.

39. A method of claim 33, wherein the chloride channel is a CLC3 channel.

40. The method of claim 39, wherein blocking the CLC3 channel results in diminished vasoconstriction to norepinephrine.

41. The method of claim 39, wherein blocking the CLC3 channel reduces penile sympathetic tone.

42. The method of claim 41, wherein the reduction of penile sympathetic tone induces an erection.

43. A method for treating erectile dysfunction comprising administering a composition comprising a CLC3 channel blocking agent or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(9) Evidence Appendix.

A. U.S. Patent No. 5,658,936.

This document was entered by the Examiner in the Office Action mailed August 24, 2004.

B. U.S. Patent No. 6,266,560.

This document was entered by the Examiner in the Office Action mailed August 24, 2004.

C. Delaney *et al.* (Delaney *et al.*, (1996) *The Breast* 5:53-54).

This document was entered by the Examiner in the Office Action mailed August 24, 2004.

D. Drug Facts and Comparisons (1997).

This document was entered by the Examiner in the Office Action mailed August 24, 2004.

E. "Erectile dysfunction" definition, the On-Line Medical Dictionary.

This document was submitted with the Amendment and Reply filed November 2, 2004, which the Examiner indicated will be entered for the purposes of appeal in the Advisory Action mailed November 26, 2004.

F. "Libido" definition, the Merriam-Webster online dictionary.

This document was submitted with the Amendment and Reply filed November 2, 2004, which the Examiner indicated will be entered for the purposes of appeal in the Advisory Action mailed November 26, 2004.